

**REMARKS**

Claims 1-93 are pending. Claims 7-11, 17-20, 32, 41-44, and 46-93 are withdrawn. Claims 22, 25, 29, 34, 36, 38, 39, and 45 are canceled herein. Therefore, claims 1-6, 12-16, 21, 23, 24, 26-28, 30, 31, and 33-40, are under consideration. Applicants have amended claim 1 to recite “correlating the number of OCP in the subject with the presence of erosive arthritis, wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis.” Additionally, claims 15, 26, 31, 33, and 35 have been amended to recite “erosive arthritis” rather than “inflammatory joint disease.” Support for the amendments to claims 1, 15, 26, 31, 33, and 35 can be found at least on page 98, line 29 through page 99 line 6 and Figure 3 where the presence on increased numbers of OCP in patients with erosive arthritis is discussed. Claim 26 has also been amended to correct an obvious grammatical error. Claim 35 has further been amended to recite “at least three or more surface markers selected from the group consisting of CD14, CD11b, CD51/CD61, RANK, CCR1, CCR4, VCAM (CD106), VLA-4 (CD49d), CD11a, MHC Class II, B7.1, B7.2, CD40, c-fms and CD16”. Support for the amendment to claim 35 can be found at least in original claims 36 and 39. Claims 40-44 have been amended to change dependencies necessitated by the amendment to claim 35. Applicants believe that these amendments do not constitute new matter nor raise new issues. Moreover, Applicants submit that these amendments were not made for reasons of patentability as the claims were clear as previously written.

**35 U.S.C. § 112, second paragraph**

Claims 1-3, 11-13, 15, 16, 21-31, 33-37, and 45 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular the Examiner alleges that claim 1 is incomplete because “claim 1 fails to specifically recite a correlation step that correlates what number or threshold levels are required in order to define an indication of IJD.” Applicants have amended claim 1 to remove recitation of “inflammatory joint disease” in favor of “erosive arthritis.” Additionally, Applicants have amended claim 1 to recite “correlating the number of OCP in the subject with the presence of erosive arthritis, wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis.”

Applicants believe that the Examiner's rejection has been addressed by Applicants' amendments and respectfully request that the rejection be withdrawn.

Additionally, the Examiner alleges that claim 2 is indefinite for the recitation of the acronym "PBMC." Applicants have amended claim 2 to recite "peripheral blood mononuclear cells (PBMC)." Applicants believe that the rejection has been overcome by Applicants' amendments and respectfully request that the rejection be withdrawn.

The Examiner has also rejected claim 2 as allegedly being indefinite for the recitation "further comprising collecting the subjects PBMC." Here, the Examiner asserts that it is "unclear what essential structural cooperative relationship exists between the collecting step in claim 2 and the measuring step in claim 1 from which it depends." Applicants have amended claim 2 to indicate to more properly recite that the OCP found in the blood of claim 1 are more specifically obtained by collecting PBMC. Applicants believe this amendment clarifies the previous language which had indicated that an additional step of collecting PBMC was conducted rather than the more appropriate indication of what portion of the blood was actually being collected. Applicants believe that in light of the amendments to claim 2, this rejection to be overcome and respectfully request its withdrawal.

The Examiner has rejected claim 15 as allegedly being indefinite for the recitation "TRAP" as well as the recitation "counting how many multinucleated cells there are producing a number of multinucleated cells in the sample." Applicants have amended claim to recite "Tartrate Resistant Acid Phosphatase (TRAP)." Additionally, Applicants have further amended claim 15 to recite "how many multinucleated cells there are in the sample from the subject" thus removing confusing language from the claim. Applicants believe that claim 15 is unambiguous as presently amended and that the rejection has been overcome by Applicants' amendments. Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claims 15, 33, and 45 as allegedly being indefinite for the recitation of "more." In particular, the Examiner asserts that "the term 'more' is not defined by the claim [and] the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the scope of the invention." The Examiner further states that the term "more is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a control subject." Applicants

respectfully point out the claim 45 is canceled herein and therefore the rejection is moot with respect to claim 45. Applicants respectfully traverse the rejection. Applicants remind the Examiner that “the fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite.” *Seattle Box Co., v Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). In fact, as stated in MPEP 2173, the primary purpose of the clarity requirement under 35 U.S.C 112, second paragraph, “is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.” Applicants note that both claims 15 and 33 provide a comparative basis for determining the presence of an increase in cells. The Examiner acknowledges in the rejection of claim 33 that such a comparative basis exist (claim 15 has the same language so this acknowledgement is true for both claims). Applicants assert that it is well within the abilities of one of skill in the art to count the number of multinucleated cells in a subject and a known control and determine if the non-control subject has a larger number of the multinucleated cells. Surely the Examiner can not be suggesting that one of skill in the art would not be able to simply count the number of cells in both subjects and determine if more cells exist in one relative to the other. Moreover, Figures 1 and 3 provides a perfect example of not only of a method one of skill in the art could accomplish this task, but also shows counting and comparison. Applicants believe this rejection has been overcome and respectfully request its withdrawal.

The Examiner has also rejected claim 25 as allegedly being indefinite for the recitation “wherein the disease is psoriatic arthritis (PsA) or Rheumatoid arthritis (RA), aseptic joint loosening of orthopedic implants, non-union of a fracture, spondyloarthropathies, psoriasis and Crohns disease.” In particular, the Examiner alleges that the language around PsA and RA is closed while the language around subsequent diseases listed “appears to improperly open up the claim to other diseases that can be detected.” Applicants respectfully point out that claim 25 has been canceled herein. Accordingly this rejection is now believed to be moot and respectfully request it be withdrawn.

The Examiner has rejected claim 26 as allegedly being incomplete for omitting allegedly essential steps. In particular, the Examiner alleges that claim 26 fails to “recite a correlation step that correlates what threshold levels of osteoclasts are required from the assay in order to define

an indication of IJD.” Applicants have amended claim 26 to recite “correlating the number of OCP in the subject with the presence of erosive arthritis.” Applicants believe that this rejection has been overcome in light of Applicants’ amendments and respectfully request that the rejection be withdrawn. Support for the amendments can be found at least on page 98, line 29 through page 99 line 6 and Figure 3 where the presence on increased numbers of OCP in patients with erosive arthritis is discussed. Additionally support for “wherein an increased number of osteoclasts in the culture from the subject relative to the number of osteoclasts in a culture of PBMC from a control subject without erosive arthritis indicates the subject has erosive arthritis” can be found in original claim 29. Applicants believe that the Examiner’s rejection has been addressed by Applicants’ amendments and respectfully request that the rejection be withdrawn.

The Examiner has rejected claim 29 as allegedly being indefinite for the recitation of “increased.” In particular, the Examiner asserts that the term “increased is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a control subject.” Applicants respectfully point out that claim 29 has been canceled. Accordingly, the rejection is moot with respect to claim 29. However, the limitations of original claim 29 have been bodily incorporated into claim 26. Therefore this rejection will be addressed in terms of claim 26. Applicants respectfully traverse the rejection. Applicants remind the Examiner that “the fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite.” *Seattle Box Co., v Industrial Crating & Packing, Inc.*, 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984). In fact, as stated in MPEP 2173, the primary purpose of the clarity requirement under 35 U.S.C 112, second paragraph, “is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.” Applicants note that both claims 26 and 1 as presently amended provide a comparative basis for determining the presence of an increase in cells. The Examiner acknowledges in the rejection of claim 26 that such a comparative basis exists. Applicants assert that it is well within the abilities of one of skill in the art to count the number of multinucleated cells in a subject and a known control and determine if the non-control subject has a larger number of the multinucleated cells. Surely the Examiner can not be suggesting that one of skill in the art would not be able to simply count the number of cells in both subjects and determine if more cells exist in one relative to the other. Moreover, Figures 1 and 3 provides a perfect

example of not only of a method one of skill in the art could accomplish this task, but also shows counting and comparison. Applicants believe this rejection has been overcome and respectfully request its withdrawal.

Furthermore, the Examiner alleges that claim 31 is indefinite for the recitation of the acronym "PBMA." Applicants have amended claim 31 to recite "PBMCI." Applicants believe that the rejection has been overcome by Applicants' amendments and respectfully request that the rejection be withdrawn.

Claim 33 is also rejected as allegedly being indefinite for allegedly not defining whether the control should be healthy and lacking antecedent basis for the recitation of "[presence of] disease." Applicants have amended claim 33 to reference "erosive arthritis" rather than inflammatory joint disease in the preamble and "disease" at the end of the claim. Support for erosive arthritis can be found at least on page 98, line 29 through page 99 line 6 and Figure 3 where erosive arthritis is discussed. Applicants believe that as presently amended antecedent basis exist for all terms in the claims. Additionally, Applicants have amended claim 33 to recite "control subject without erosive arthritis." Support for this amendment to claim 33 can be found at least on page 98, line 29 through page 99 line 6 and Figure 3 where the use of controls without erosive arthritis are discussed. Applicants believe that in light of these amendments, this rejection has been overcome and respectfully request the rejection be withdrawn.

Additionally, the Examiner alleges that claim 36 is indefinite for the improper recitation of Markush language in reciting "selected from the group consisting of ...and or..." Claim 36 has been canceled herein. Accordingly, this rejection is now moot.

Applicants believe these rejections have been overcome and respectfully request their withdrawal.

#### **Double Patenting**

Claims 1-3, 12-16, 21-26, and 33-36 have been objected to under 37 C.F.R. § 1.75 as allegedly being a substantial duplicate of and provisionally rejected to under 35 U.S.C. § 101 as allegedly constituting double patenting in view of claims 1-3, 11-13, 15, 16, 21-26, and 33-36 of U.S. Application No. 10/548,389. Applicants acknowledge the rejection and will formally respond to the provisional double patenting rejection in the appropriate application once claims are found to be allowable necessitating the removal of the provisional status of the rejection.

Regarding the objection under 37 C.F.R. § 1.75, Applicants respectfully point out that the Examiner has misapplied the rule. As noted by the Examiner 37 C.F.R. § 1.75 refers to the situation where “two claims in AN application are duplicates or else so close in content that they both cover the same thing.” [emphasis added] Thus, the rule applies to situations where two claims in the SAME application are substantially similar or identical. 37 C.F.R. § 1.75 does NOT refer to situations where claims in different applications are duplicates. Accordingly, the Examiner has misapplied the rule and has not pointed to any two claims in the present application that are identical or at a minimum substantially similar. Applicants believe this objection has been overcome and respectfully request its withdrawal.

**35 U.S.C. § 102(a)**

Claims 1-6, 12, 14, 21-28, 30, 34-36, 38-40, and 49 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Hirayama et al. (2002) *Rheumatology* 41:1232-1239. Applicants respectfully point out that claim 49 has been withdrawn from consideration and claims 25, 34, 36, 38, and 39 have been canceled; therefore, the rejection is moot with respect to these claims. Applicants respectfully point out that in order for a reference to anticipate the claim, it must teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants have amended claims 1 and 26 to recite “correlating the number of OCP in the subject with the presence of erosive arthritis, wherein an increase in the number of OCP in the subject relative to a control subject indicates the presence of erosive arthritis.” Applicants respectfully point out that Hirayama et al. does not disclose let alone teach correlating erosive arthritis with an increase in the number of OCP relative to a control without erosive arthritis as claimed herein. In fact, nowhere in Hirayama specifically states any association of the number of OCP with erosive arthritis. Accordingly Hirayama fails to teach each and every limitation of the claim. Because each and every limitation of the claim is not taught by Hirayama, the reference can not anticipate the claim. Applicants believe that in light of the amendments made to claims 1 and 26, this

rejection has been overcome. Applicants respectfully request that the rejection be withdrawn with respect to these claims and their dependencies.

Regarding claims 35 and 40, Applicants respectfully point out that claim 35 has been amended to recite a method of determining whether a subject has erosive arthritis comprising among other things “probing for three or more surface markers of mononuclear OCP, wherein the surface markers are selected from the group consisting of CD14, CD11b, CD51/CD61, RANK, CCR1, CCR4, VCAM (CD106), VLA-4 (CD49d), CD11a, MHC Class II, B7.1, B7.2, CD40, c-fms and CD16.” As noted above, for a claim to be anticipated, each and every limitation must be taught by the art. Importantly, nowhere in Hirayama et al. is a determination of erosive arthritis made by probing for three or markers from the list enumerated in claim 35. Accordingly Hirayama fails to teach each and every limitation of the claim. Because each and every limitation of the claim is not taught by Hirayama, the reference can not anticipate the claim. Applicants believe that in light of the amendments made to claim 35 this rejection has been overcome and respectfully request its withdrawal.

Claims 1-5, 12, 14, 21, 23-28, 34-36, 38 and 39 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Jevon et al. (2003) *Scand J. Rheumatol.* 32:95-100. Applicants respectfully point out that claims 25, 34, 36, 38, and 39 have been canceled; therefore, the rejection is moot with respect to this claim. Applicants respectfully traverse the rejection. Applicants respectfully point out that in order for a reference to anticipate the claim, it must teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants have amended claims 1, 34, and 35 to recite that the subject has “erosive arthritis.” Applicants respectfully point out that Jevon et al. does not disclose let alone teach erosive arthritis as claimed herein. Accordingly Jevon fails to teach each and every limitation of the claim. Because each and every limitation of the claim is not taught by Jevon, the reference can not anticipate the claim. Applicants believe that in light of the amendments made to claims 1 and 26, this rejection has been overcome. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

**35 U.S.C. § 103**

Claims 13, 15, 16, 29, 31, 33, 36, 37, and 45 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Hirayama et al. in view of Li et al. (2002) *J. Bone and Mineral Research*. JBMR Program and Abstracts 2002. Applicants respectfully point out that claims 29, 36, and 45 have been canceled; therefore, the rejection is moot with respect to these claims. Applicants respectfully traverse the rejection. In the recent *KSR Int'l Co. v. Teleflex, Inc.* ruling, the Supreme Court has reaffirmed the *Graham* factors for determination of obvious under 35 U.S.C. 103(a). *KSR Int'l Co. v. Teleflex, Inc. (KSR)*, No 04-1350 (U.S. Apr. 30, 2007). The three factual inquiries under *Graham* require examination of: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art. *Graham v. John Deere (Graham)*, 383 U.S. 1, 17-18, 149 USPQ 459, 467 (1966). Additionally, the court in *Graham* noted a fourth consideration for the determination of obviousness would be any objective evidence of secondary considerations such as unexpected results, unmet need in the art, and commercial success.

Applicants respectfully point out that in order to render a claim obvious all the limitations must be disclosed by the combination of references as well as the general knowledge in the art. As noted above, Hirayama does not teach a step of correlating the number of OCP with the presence of erosive arthritis. Accordingly, the Examiner must rely on Li to teach that an increased number of OCP relative to a control without erosive arthritis indicates the presence of erosive arthritis. As noted by the Examiner, Li et al merely teaches that TNF $\alpha$  is an osteoclastogenic factor and is important along with RANK/RANKL in the process of OCP differentiation. Li et al does not teach the number of OCP is increased in subjects with erosive arthritis. Moreover, Applicants note that neither Hirayama or Li teach a method of determining the presence of erosive arthritis comprising among other things probing with three or more markers from the list enumerated in claim 35. Thus alone or in combination, the art fails to teach all the limitations of the claims. For this reason alone the claims are not obvious.

Furthermore, Applicants respectfully point out that on page 1237, column 1, paragraph 1 of Hirayama, the authors note that "As assessed by TRAP+ MNC formation in PBMC cultures, RA patients did **NOT** have more circulating osteoclast precursors in the monocyte fraction."



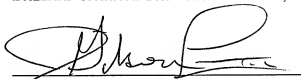
[emphasis added] This is the exact opposite of the finding herein. As noted in KSR, "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." KSR at 1395. Because Hirayama specifically teaches away from the claimed invention, it can not render the claimed methods obvious. For this reason alone this rejection has been overcome. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment authorizing payment in the amount of \$555.00 the large entity fee under 37 C.F.R. § 1.17(a)(3) for a three (3) month Extension of Time and a Request for Extension of Time are being submitted electronically. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF EFS-WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted by EFS-WEB on the date indicated below.



J. Gibson Lanier

Date

10/29/08